3D printing: Engineering novel oral devices with unique design and drug release characteristics

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Abstract

Three dimensional printing (3DP) was used to engineer novel oral drug delivery devices, with specialised design configurations loaded with multiple actives, with applications in personalised medicine. A filament extruder was used to obtain drug-loaded - paracetamol (acetaminophen) or caffeine - filaments of polyvinyl alcohol with characteristics suitable for use in fused-deposition modelling 3D printing. A multi-nozzle 3D printer enabled fabrication of capsule-shaped solid devices, containing paracetamol and caffeine, with different internal structures. The design configurations included a multilayer device, with each layer containing drug, whose identity was different from the drug in the adjacent layers; and a two-compartment device comprising a caplet embedded within a larger caplet (DuoCaplet), with each compartment containing a different drug. Raman spectroscopy was used to collect 2-dimensional hyper spectral arrays across the entire surface of the devices. Processing of the arrays using direct classical least squares component matching to produce false colour representations of distribution of the drugs showed clearly the areas that contain paracetamol and caffeine, and that there is a definitive separation between the drug layers.

Drug release tests in biorelevant media showed unique drug release profiles dependent on the macrostructure of the devices. In the case of the multilayer devices, release of both drugs was simultaneous and independent of drug solubility**.** With the DuoCaplet design it was possible to engineer either rapid drug release or delayed release by selecting the site of incorporation of the drug in the device, and the lag-time for release from the internal compartment was dependent on the characteristics of the external layer. The study confirms the potential of 3D printing to fabricate multiple-drug containing devices with specialized design configurations and unique drug release characteristics, which would not otherwise be possible using conventional manufacturing methods.

1. Introduction

3D printing (3DP) is a new manufacturing technique, which builds up solid objects by deposition of many thin layers. 3DP is now used as a production tool or for rapid prototyping in many diverse fields, including the aerospace industry, architecture, nanosystems, fashion and biomedical research and it is destined to be the next industrial revolution changing the way many things are created, transported and stored. Nowadays, design templates can be downloaded from the internet and objects printed at home, while medical researchers are using 3D printing to create functional organs or bones [1-5].

In the pharmaceutical field, the future of medicine design and manufacture may move away from industrial production of tablets/capsules of limited dose range towards in situ fabrication of unit dosage forms with doses and/or drug combinations tailored to the patient [6]. To face these challenges, pharmaceutical research has to evaluate, develop and adapt these novel productive technologies to the high quality requirements demanded and regulated by the pharmaceutical industry.

There are many types of 3D printers commercially available, but fused-deposition modelling (FDM) offers possibly the most immediate potential to unit dose fabrication. In FDM 3DP an extruded polymer filament is passed through a heated nozzle that softens the polymer and it is then deposited on a build plate, in the x-y dimensions, creating one layer of the object to be printed. The build plate then lowers and the next layer is deposited. In this fashion, an object can be fabricated in three dimensions, and in a matter of minutes. FDM 3DP technology allows printing of a wide range of polymers and has the significant advantage of relatively low cost (average cost of a FDM 3D printer 500-2000 USD). The printer feedstock is an extruded polymer filament usually, 1.75 or 3 mm in diameter, and one of the prime benefits of FDM 3DP is that it is possible to blend drug and polymer into a solid dispersion prior to extrusion, to print drug-loaded dosage forms.

The manufacture of drug-loaded filament has been demonstrated with different drugs by soaking a water-soluble filament in a concentrated ethanolic solution of the drug: e.g. for fluorescein [7], 4-aminosalicylic acid (4ASA) and 5-aminosalicylic acid (5-ASA) [8] and prednisolone [9]. However, in all of these studies the percentage of drug loading is low, because the drugs were loaded by passive diffusion from solution. An alternative method is to incorporate drug into polymer filaments by hot-melt extrusion (HME), a widely used technique in the pharmaceutical industry, in which the raw materials are forced to mix in a rotating screw at elevated temperatures before being extruded through a die to produce a strand of uniform characteristics [10]. HME has been reported as a viable method to prepare a wide range of drug delivery

systems, including fast or modified release solid dosage forms, granules, pellets, transdermal patches, transmucosal films and implants [11-13]. The use of HME to produce drug-loaded 3D printable filaments has been also shown to be achievable for water-soluble filaments to fabricate oral dosage forms [14] and for plastics used for medical devices [15].

Combination drug therapy is common for treating diseases like cancer, diabetes, cardiovascular conditions and infections and in many cases drugs are combined in the same dosage form for convenience and to improve compliance. The combinations are usually manufactured as immediate release formulations of fixed dose; however, the selected dose or the simultaneous release of the drugs may not be optimal for absorption or for getting the desired therapeutic effect [16]. A potential benefit of FDM 3DP is that the printer can be used to fabricate tablets incorporating different drugs by printing different filaments simultaneously. The manufacture of bi-layer tablets loaded with guaifenesin has been previously reported using a multiple syringe-based deposition 3D printer [17]. Theoretically computer aided design could leave imagination and the resolution of the 3D printer as the only limits to the design and manufacture of complex, multi-faceted tablets. Multi-drug 3D printing would allow incorporation in one dose of several drugs (even if incompatible with each other as they could be contained within discrete polymers) with modified/controlled drug release and of doses tailored to the patient.

In all of the previous studies of 3DP FDM only one drug was incorporated at each time into the printed tablet. To move things forward, the feasibility of incorporating two drugs was addressed in this study. To this end, two drugs often found in combination in commercial medicines in are paracetamol (acetaminophen) and caffeine. Paracetamol is effective at relieving mild to moderate pain and fever, and caffeine is a mild stimulant that helps reduce fatigue, and it is also thought to enhance the painkilling effect of paracetamol [18].

The aims of this work therefore are to (i) produce different filaments containing paracetamol or caffeine in a water soluble polymer (polyvinyl alcohol, PVA) suitable for printing into pharmaceutical dosage forms and (ii) to print with a dual FDM 3D printer a diverse range of multi-layer capsule-shaped devices with modified drug release profiles to meet the needs of specific therapies. The effect of the internal structure (3D design) on the drug dissolution behaviour in biorelevant media is also evaluated.

2. Materials and methods

Commercial soluble filament made of polyvinyl alcohol (PVA) was purchased from Makerbot Inc., USA (1.75mm diameter, print temperature 190-220°C, batch No: 20140509-1,). Paracetamol (MW 151.16, solubility at 37ºC: 21.80 g/L [19]) and caffeine (MW 194.19, solubility at

37ºC: 37.07 g/L [19]), both USP grade, were purchased from Sigma-Aldrich, UK (Figure 1). The salts for preparing the buffer dissolution media were purchased from VWR International Ltd., Poole, UK.

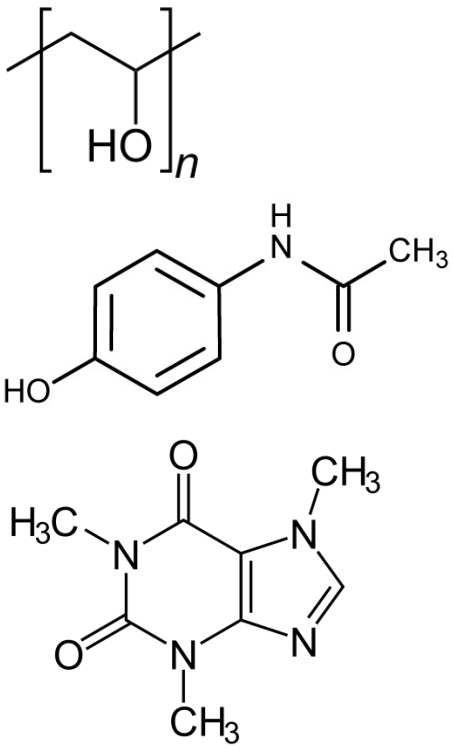


Figure 1. Chemical structure of PVA, paracetamol and caffeine.

2.1 Preparation of PVA filament loaded with drug

The PVA filament was cut into small pieces (~1 mm) using a Pharma 11 Varicut Pelletizer (Thermo Fisher Scientific, UK), milled in a Wahl ZX789 grinder (Wahl store, UK) and sieved through a 1000 µm mesh. The milled PVA was mixed in a mortar and pestle with drug, (paracetamol or caffeine), until no agglomerated particles of drug or polymer were seen, and then placed for 10 minutes in a Turbula® T2F shaker-mixer (Glen Mills Inc., USA). The selected theoretical drug contents of the mixtures were 5 or 10% w/w for each drug. The mixture of drug and PVA was then extruded using a single-screw filament extruder, Noztec Pro hot melt extruder (Noztec, UK) in order to obtain a filament with the drug loaded (temperature 180 °C, nozzle diameter 1.75 mm, screw speed 15 rpm). The extruded filaments obtained were protected from light and kept in a vacuum desiccator until printing. The drug-loading of the filaments was determined by HPLC analysis.

2.2. Printing dosage forms

Oral drug delivery devices were fabricated from the drug-loaded filaments using a standard fused-deposition modelling 3D printer, MakerBot Replicator 2X (MakerBot Inc, USA). The templates used to print the devices were designed with AutoCAD 2014® (Autodesk Inc., USA) and exported as a stereolithography file (.stl) into the 3D printer software (MakerWare v. 2.4.1, MakerBot Inc., USA). The .stl format encodes only the surface data of the object to be printed and requires the thickness of the surface, the infill and the temperature to be defined in order to print the desired object. The infill percentage was 100% in order to produce solid dosage forms of high density and other printer settings were as follows: standard resolution with the raft option deactivated and an extrusion temperature of 200 °C, speed while extruding (90mm/s), speed while traveling (150mm/s), number of shells (2) and layer height (0.20mm). The basic selected 3D geometry was a size 4 capsule-shaped tablet, 14.30mm length x 5.30mm diameter (Figure 2). The layers of the devices were varied in the 3D template to get three different types of oral devices: (i) multi-layer oral devices with alternate (1mm thick) layers of paracetamol and caffeine (Figure 2 A) and (ii) DuoCaplets with a capsule-shaped core (9.00mm length x 3.34mm diameter) incorporating the opposite model drug to the one on outer coat (Figure 2 B). In all cases, four devices were printed at the same time.

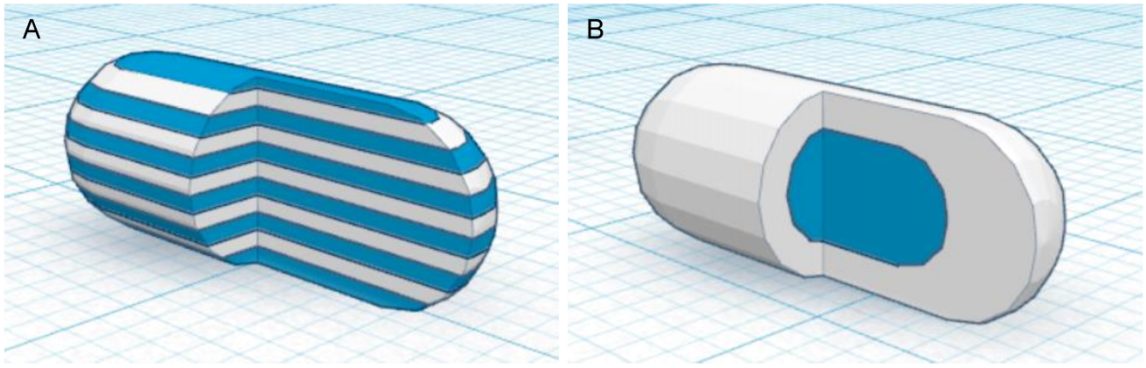


Figure 2. 3D representation of the printed solid dosage forms: (A) sectioned multilayer device and (B) sectioned DuoCaplet (caplet in caplet).

2.3 Thermal analysis

Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) were used to characterise the filaments and single drug loaded 3D printed caplets. DSC measurements were performed with a Q2000 DSC (TA instruments, Waters, LLC, USA) at a heating rate of 10°C/min. Calibration for cell constant and enthalpy was performed with indium (Tm = 156.6°C,

∆Hf =28.71 J/g) according to the manufacturer instructions. Nitrogen was used as a purge gas with a flow rate of 50 mL/min for all the experiments. Data were collected with TA Advantage software for Q series (version 2.8.394), and analysed using TA Instruments Universal Analysis 2000. All melting temperatures are reported as extrapolated onset unless otherwise stated. TA aluminium pans and lids (Tzero) were used with an average sample mass of 8-10mg.
For TGA analysis, samples were heated at 10°C/min in open aluminium pans with a Discovery TGA (TA instruments, Waters, LLC, USA). Nitrogen was used as a purge gas with a flow rate of 25 mL/min. Data collection and analysis were performed using TA Instruments Trios software and % mass loss and/or onset temperature were calculated.

2.4 X-ray powder diffraction (XRPD)

Discs of 23mm diameter x 1mm height made from PVA filaments or drug-loaded PVA filaments were 3D printed and analysed. Samples of pure caffeine and paracetamol were also analysed. The X-ray powder diffraction patterns were obtained in a Rigaku MiniFlex 600 (Rigaku, USA) using a Cu Kα X-ray source (λ=1.5418Å). The intensity and voltage applied were 15 mA and 40 kV. The angular range of data acquisition was 3–60° 2θ, with a stepwise size of 0.02° at a speed of 5°/min.

2.5 Device morphology characterisation

The physical dimensions of the devices were measured using a digital calliper. Pictures of the devices were taken with a Nikon CoolpixS6150 with the macro option of the menu.

2.6 Raman spectroscopy and mapping

Samples were mounted and focused using a x5 objective on a Renishaw InVia Raman microscope equipped with a 300 mW 785 nm HPNIR Renishaw laser. Spectral arrays were acquired with 9500 spectra recorded over the surface of the sample using a step size of 56.7µm in X and Y. A 1200 line grating was used providing spectral resolution up to 1 cm^{-1}.
Processing was performed in Renishaw WiRE software v.4.2 using cosmic ray removal (nearest neighbor method) followed by direct classical least squares (DCLS) component matching to paracetamol and caffeine reference spectra to generate 2-dimensional false colour maps.

2.7 Determination of drug loading

A caplet or a section of drug-loaded strand (approx. 0.3g) was placed in a volumetric flask with deionized water (1L) under magnetic stirring until complete dissolution (n=2). Samples of the

solutions were then filtered through 0.45 µm filters (Millipore Ltd, Ireland) and the concentration of drug determined with HPLC (Hewlett Packard 1050 Series HPLC system, Agilent Technologies, UK). The validated high performance liquid chromatographic assay entailed injecting 20 µL samples for analysis using a mobile phase, consisting of gradient system of (A) water adjusted to pH 2 with orthophosphoric acid and (B) acetonitrile, through a Luna 5µm C18 column, 150 x 4.6 mm (Phenomenex, UK) maintained at 40 °C. The mobile phase was pumped at a flow rate of 1 mL/min under the following gradient program: 0-15 min, 5-20% B; 15-16 min, 20-5% B. The eluent was screened at a wavelength of 247 nm, retention times were 7.0 min for paracetamol and 10.4 min for caffeine. All measurements were made in duplicate.

2.8 Dissolution test conditions

The drug dissolution profiles from the formulations were obtained using a USP-II apparatus (Model PTWS, Pharmatest, Hainburg, Germany). Slightly modified dissolution settings of previous studies were followed to simulate the environment conditions of the fasted GI tract [20, 21]. Briefly, the devices were placed for 1 h into 900 mL of 0.1 M HCl, which simulates gastric residence time; and subsequently into 950 mL of modified Hanks (mHanks) based dynamic physiological dissolution medium for 35 min (pH 5.6 to 7); then in 1000 mL of modified Krebs buffer (pH 7 to 7.4 and then to 6.5). The modified Hanks buffer based dissolution media [22] (136.9 mM NaCl, 5.37 mM KCl, 0.812 mM $MgSO_4.7H_2O$, 1.26 mM $CaCl_2$, 0.337 mM $Na_2HPO_4.2H_2O$, 0.441 mM KH_2PO_4, 4.17 mM $NaHCO_3$) forms an in-situ modified Kreb's buffer [23] by addition of 50 mL of pre-Krebs solution (400.7 mM $NaHCO_3$ and 6.9 mM KH_2PO_4) to each dissolution vessel.

The 3.5 h in bicarbonate buffer (pH 5.6 to 7.4), represents the transit time through the small intestine, followed by a drop in buffer pH (6.5), which represents the colonic environment, were selected to simulate the conditions for intestinal transit of pharmaceutical formulations and pH values in different segments of the GI tract in a representative fasted individual. The buffer capacity and ionic composition of the physiological bicarbonate buffers representing the different regions of the GI tract closely match the buffer capacities of the intestinal fluids collected from the different parts of the gut in humans [20-23].

The media are primarily a bicarbonate buffer in which bicarbonate (HCO_3^-) and carbonic acid (H_2CO_3) co-exist in an equilibrium, along with CO_2 (aq) resultant from the dissociation of the carbonic acid. The pH of the buffer system can be can be decreased by purging CO_2 (g) in the

solution, which promotes the formation of carbonic acid. Similarly, an inert gas (such as Helium), which removes the dissolved CO_2 from the solution, reduces the pH of the media. The purging of gases is controlled by an Auto pH System^{TM} [24], which consists of a pH probe connected to a source of carbon dioxide gas (pH reducing gas), as well as to a supply of helium (pH increasing gas), controlled by a control unit. The control unit is able to provide a dynamically adjustable pH during testing (dynamic conditions) and to maintain a uniform pH value over the otherwise unstable bicarbonate buffer pH.

The paddle speed of the USP-II was fixed at 50 rpm and the tests were conducted at 37 +/- 0.5 °C (n=3). The percentage drug released from the formulations was determined using an in-line UV spectrophotometer (Cecil 2020, Cecil Instruments Ltd., Cambridge, UK) at 244 nm (paracetamol) or 274 nm (caffeine). Data were processed using Icalis software (Icalis Data Systems Ltd, Berkshire, UK), and concentrations of each drug were calculated based on the input of absorbance of each drug on the total absorbance at the selected wavelengths. Additionally, to validate the calculus, 1mL sample of the dissolution media was withdrawn every hour and the drug concentrations were determined by HPLC.

3. Results and discussion

It was possible to produce drug loaded filaments of PVA by HME incorporating paracetamol or caffeine that were suitable for 3D printing. Filaments were not significantly different from the commercial PVA filament in terms of size (diameter), physical appearance and mechanical behaviour.

The drug loadings of the four PVA filaments were 4.3% and 8.2% for paracetamol and 4.7% and 9.5% for caffeine. The attempt to incorporate higher drug loading percentages reduces, at some point, the quality of the filament making it not appropriate for 3D printing, although the use of other excipients as plasticizer could help to obtain considerably higher drug loading percentages than 10% w/w.

TGA data of drug loaded filaments show no sign of drug degradation (Figure 3). The weight loss up to 200°C was between 4 and 5.5%w/w for all the filaments. The average weight loss for plain polymer filaments was 5 ± 2%, as the decomposition of PVA is reported to start above 250°C [25], this is mass loss could be attributed to the evaporation of water. The mass loss noticeable for the active compounds alone could be related to the first stage of decomposition and/or sublimation. However, the extent of this is greatly reduced in the formulations as shown in the

TGA curves for the drug-loaded filaments. The most likely reason for the actual drug loading being slightly lower than the theoretical amount is adhesion of the fine drug powder to the container during the mixing process and to the walls of the barrel of the HME during the extrusion process. Nevertheless, in this study it has been possible to attain higher drug loading yield than in a previous work by obtaining mixtures of drug and polymer of more comparable particle size, 4.30% w/w paracetamol loading versus the 3.95% w/w for the same 5% theoretic formulation [14]. The optimization of the procedure could establish the filament extruder as a cheaper alternative to the twin-screw HME apparatus typically used for production in the pharmaceutical industry.

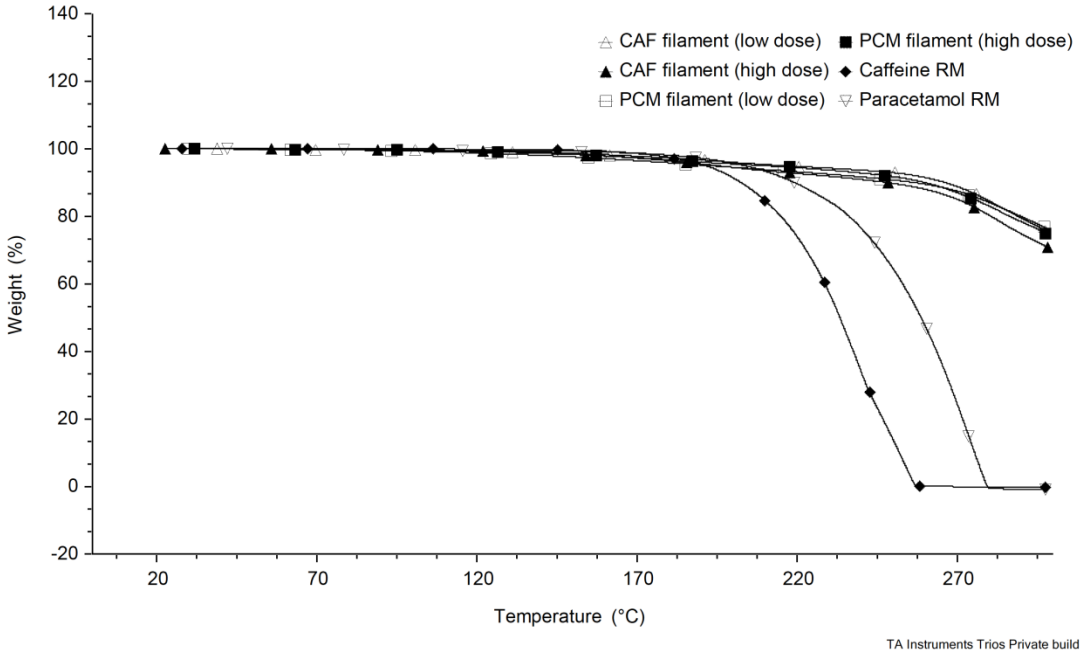


Figure 3. TGA results for caffeine (CAF) and paracetamol (PCM) loaded filaments (RM: raw material).

Secondly, it was possible to manufacture oral drug delivery devices of different layers by dual 3D printing with the loaded filaments, Figure 4. Here, we printed two different types of devices obtained from the drug loaded filaments: multilayer devices and DuoCaplets (caplet in a caplet). The mechanical properties of the devices were satisfactory, and the devices were not friable and easy to handle. As reported in previous studies[7, 8], the caplets showed a plastic-like aspect with an incredibly high tablet strength impossible to quantify with a traditional tablet hardness

tester. The friability of all the formulations was zero, and it was not possible to separate different layers applying forces with sharp surfaces or human nails, without actually cutting the layers.

The evaluation of the drug loading from caplets showed similar values to the individually drug–loaded filaments used for printing, indicative of no degradation during the 3DP process.

Figure 4. Images of the 3D printed caplets: from left to right, multilayer device of 8.2% paracetamol-PVA 9.5% caffeine-PVA, DuoCaplet of 9.5% caffeine-PVA (outer) 8.2% paracetamol-PVA (core) and DuoCaplet of 8.2% paracetamol-PVA (outer) 9.5% caffeine–PVA (core)

The geometry of the 3D printed devices was selected to recreate the characteristics of size and shape of a size 4 capsule. This geometry is more realistic than that used in previous work, where authors designed flat tablets that are easier to print due to the high surface area in contact to the building plate [7-9, 17], although the possibility of manufacture more intricate shapes has been reported [14]. The arched and oblong shapes of the 3D printed devices are easier to swallow for the patient than flat round tablets [26]. The process of printing four devices at the same time reduces the variability in both size and weight, compared with previous works [7, 8], which would suggest the idea of printing several dosage forms per batch could be better in terms of variability than printing one by one (Table 1).

Table 1. Measured parameters of the 3D printed devices

Drug loading	Formulation	Weight (mg)	Height (mm)	Width (mm)	Length (mm)
Low dose	Multilayer paracetamol-caffeine	269.3 ±13.9	5.20 ±0.03	5.32 ±0.07	14.18 ±0.11
	DuoCaplets caffeine core	246.2 ±16.7	5.39 ±0.01	5.11 ±0.07	14.07 ±0.05
	DuoCaplets paracetamol core	273.5 ±18.0	5.34 ±0.01	4.92 ±0.07	13.92 ±0.17
High dose	Multilayer paracetamol-caffeine	257.1 ±8.7	5.32 ±0.03	5.25 ±0.03	14.12 ±0.11
	DuoCaplets caffeine core	224.5 ±10.8	5.37 ±0.09	5.02 ±0.09	14.00 ±0.04
	DuoCaplets paracetamol core	229.8 ±20.6	5.37 ±0.04	5.01 ±0.10	13.90 ±0.14

FDM appears to be a versatile approach suitable for manufacturing formulations with multiple layers of different composition. Although two drugs were used in this study, the use of 3D printers with more nozzles would allow incorporation of more drugs or excipients. The different layers of the multilayer devices are welded independently of the nature of the layers, making them difficult to separate. It is important to highlight this because insufficient bilayer hardness and layer bonding are typical drawbacks using conventional bilayer technology[27]. The use of the 3D printing technology to DuoCaplets or multilayer dosage forms allows accurate individual layer weight control, simply by changing parameters in the software. This technology would allow in the future the fabrication of formulations with different geometries [14] combining layers incorporating different drugs (even incompatible) with different doses for a personalized treatment.

Raman spectroscopy has been used to collect 2-dimensional hyper spectral arrays across the entire surface of the devices. Interrogation of individual spectra at the cross section of the devices incorporating both drugs indicates that paracetamol is present as amorphous phase within the polymer matrix, whereas caffeine is in a crystalline form. Processing of the arrays using DCLS component matching to produce false colour representations of distribution (Figure 5) shows clearly the areas that contain paracetamol and caffeine, and that there is a definitive separation between the layers.

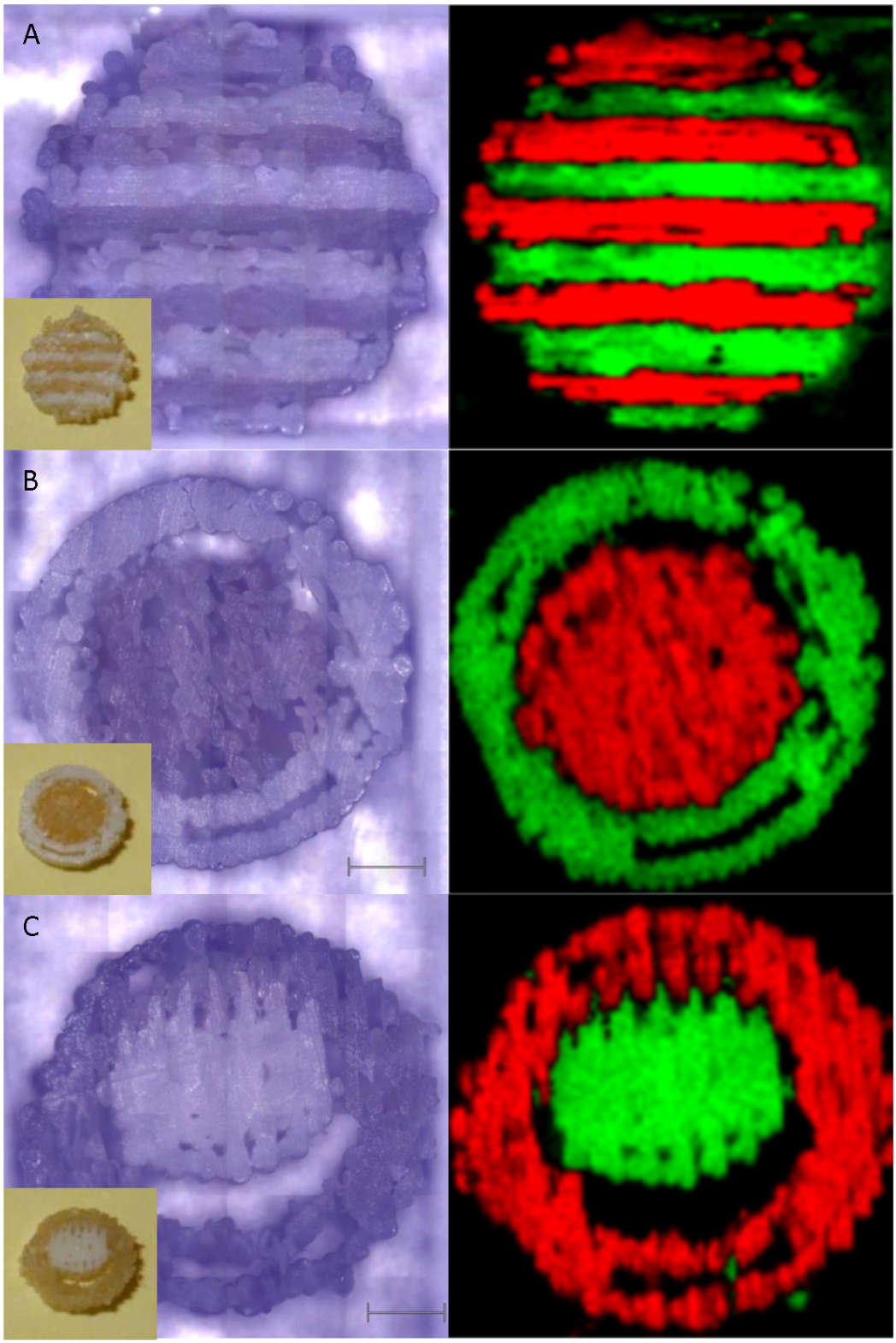
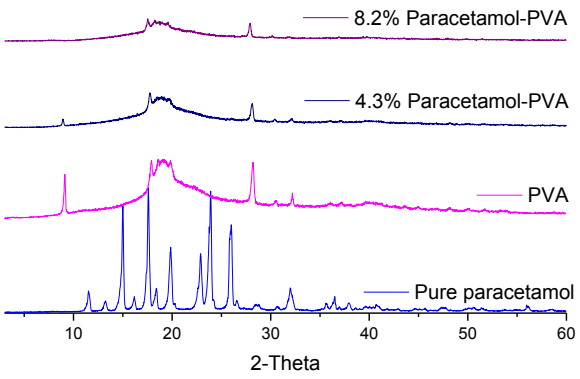


Figure 5. White light and 2-dimensional Raman mapping images of the cross-section of the caplets from (A) multilayer device of 8.2% paracetamol-PVA 9.5% caffeine-PVA, (B) DuoCaplet

of 9.5% caffeine-PVA (outer) 8.2% paracetamol-PVA (core) and (C) DuoCaplet of 8.2% paracetamol-PVA (outer) 9.5% caffeine–PVA (core). Caffeine – green and paracetamol – red.

XRPD confirms that caffeine is present in a crystalline form in the printed formulations at both 4.7 and 9.5% (Figure 6). This is supported by DSC data where the melting point of PVA shows a shoulder which suggests that the melting point of the polymer is reduced by caffeine and this reduction is more profound with the 9.5% drug content (Figure 6). The melting point of caffeine is around 235°C so it should be solid around the melting point of PVA.

A


8.2% Paracetamol-PVA
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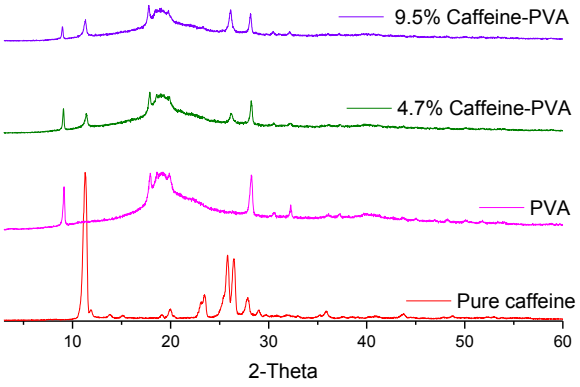
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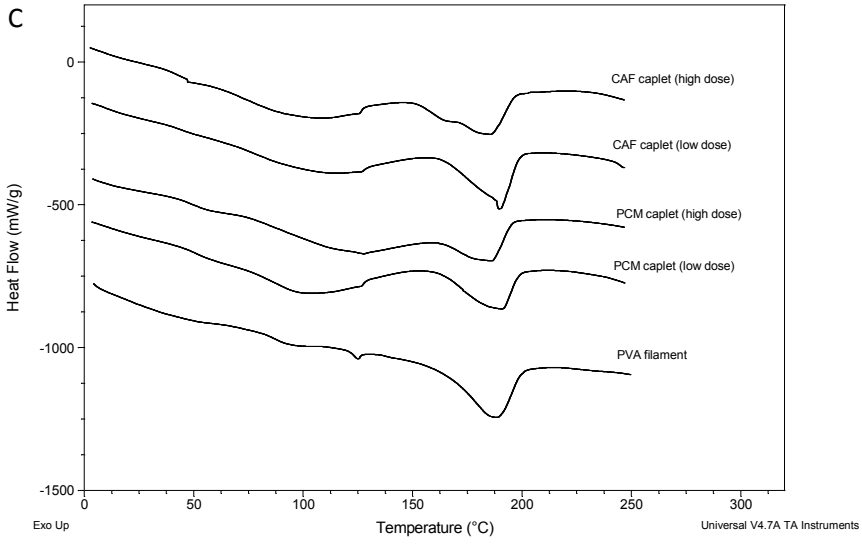
0
-500
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Heat Flow (mW/g)
CAF caplet (high dose)
CAF caplet (low dose)
PCM caplet (high dose)
PCM caplet (low dose)
PVA filament
0
50
100
150
200
250
300
Exo Up
Temperature (°C)
Universal V4.7A TA Instruments

Figure 6. X-ray powder diffractograms (A) of pure paracetamol and 3D printed discs of PVA, 4.3% paracetamol-PVA and 8.2% paracetamol-PVA and (B) of pure caffeine and 3D printed discs of PVA, 4.7% caffeine-PVA and 9.5% caffeine-PVA; (C) DSC thermograms for single loaded paracetamol (PCM) or caffeine (CAF) 3D printed caplets.

XRPD data do not show any extra peaks in the patterns of paracetamol formulations at both levels of drug loading. This confirms that the drug is present in an amorphous phase within the polymer matrix as reported before. It is noticeable that the crystallinity of PVA appears to reduce with increasing the drug loading which support the suggestion of formation of a solid dispersion of the drug and the polymer. DSC data show the glass transition (Tg) of PVA is reduced from ~85 to 45 ^{o}C with and without paracetamol, respectively (Figure 6). This also supports the idea of formation of solid dispersion.

On the other hand, caffeine appears to be in the crystalline form as shown in Figure 6B. It is also evident from the XRPD data that the polymorphic form in the printed formulation is different from that of the pure form as indicated by the peak at around 26degree in the patterns for the printed discs. This suggests that the drug, which has a high melting point of about 235degrees, dissolves in the molten polymer during printing and then recrystallized as the printed polymer and drug mix solidifies upon cooling to a different form.

The difference in the interaction of the two drugs with PVA could be the reason for this difference in the physical form of the drug in the formulations. Hydrogen bonding is the most common way of interaction between drugs and polymers [28, 29]. PVA has an -OH group in its structure, which is available for such interaction [29]. The structures of paracetamol and caffeine (Figure 1) show that caffeine has limited H-bonding potential through N4 as the surrounding methyl groups sterically hinder the carbonyl groups. On the contrary, paracetamol has more than one possible position for H-bond formation.

Dissolution tests of the different formulations performed under biorelevant conditions show a diverse variety of release profiles that confirm that the different structures play an important role in defining release kinetics (Figure 7).

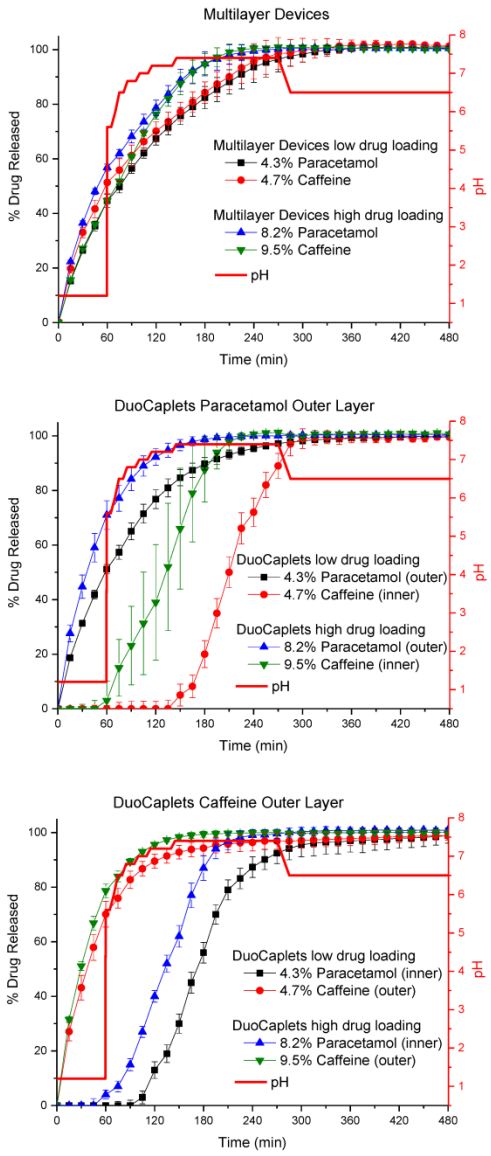

Figure 7. Drug dissolution profiles from 3DP caplets: multilayer devices of paracetamol and caffeine; DuoCaplets with paracetamol in the outer layer and caffeine in the core; and DuoCaplets with caffeine in the outer layer and paracetamol in the core. Red line shows the pH values of the media.

The dissolution results for multilayer devices show quite similar drug dissolution profiles, reaching 100% drug release in less than 360min. Drug release starts in the gastric phase (acid medium) and continues in the intestinal phase (biorelevant bicarbonate buffers), independently

of the nature or pH of the dissolution media. The release of the two drugs incorporated in each device happens at the same time and no differences from the effect of the solubility of the drug were observed. This is especially evident after 90min when the dissolution profiles for paracetamol and caffeine from each kind of multilayer device are the same. The increase of the drug loading increases the drug release rate of both drugs, probably due to the lower percentage of the PVA matrix that is in charge of effectively controlling drug release. In previous works, drug release from similar kinds of 3D printed formulations evaluated in different media with different drugs was reported to be regulated through an erosion-mediated process [7, 14]. This multilayer system may effectively be used to release different drugs following the same release pattern or to deliver chemically incompatible drugs, because they can be isolated in different sections of the drug delivery device.

Drug release profiles from the DuoCaplets are the most interesting and promising for delayed/controlled release (Figure 7). In these systems the drug incorporated in the external layer is released first and release of the drug in the internal layer only commences when the external layer is practically dissolved. At least 50% of the drug in the external layer is released in the gastric phase of the dissolution (this percentage is higher than 80% if the drug is caffeine). The drug in the internal core is released after a lag time of 50 to 135 min through the small intestinal phase of the dissolution test. Longer lag times were obtained when paracetamol was incorporated in the external layer and the drug loading was lower, due to a slower erosion-dissolution rate of the layer, as aforementioned for the standard single loaded caplets. Drug release from water soluble and swellable polymers is basically governed by the relative contribution of two mechanisms, drug diffusion and polymer dissolution (surface erosion) [30]. The contribution of each mechanism depends on different factors such nature of the excipients and drug solubility. Previous studies with 3D printed PVA tablets reported that an erosion-mediated process governed the dissolution process [7, 8], whereas further studies have to be done to show there is no diffusion of the drug loaded in the core through the external layer before the erosion-dissolution of the external layer is completed. Here we observed the effect of drug and the drug percentage in the external layer on the dissolution of the core, but other parameters such as thickness could be modified to change the drug release on the internal caplet.

The dissolution data from the different dosage forms do show that it is very feasible to design devices with controlled-drug release profiles of two drugs by careful selection of the internal structure of the devices (standard caplets, multilayer devices and DuoCaplets).

Conclusions

Four filaments of PVA incorporating paracetamol (4.3 and 8.2%) or caffeine (4.7 and 9.5%) were successfully obtained using a filament extruder with appropriate characteristics for use in FDM 3DP. The printer software enabled easy fabrication of oral drug delivery devices with different inner structures (multilayer device and DuoCaplet), which would be challenging to manufacture by powder compaction, demonstrating the potential of 3DP as a novel manufacturing technology in pharmaceutics. Raman mapping showed clearly the areas that contain paracetamol and caffeine, and that there is a definitive separation between the different drug layers.

Drug release test in biorelevant media showed characteristic drug release profiles from the different devices depending on the macrostructure of the devices. In multilayer devices incorporating two drugs the drug release rate was similar for both drugs but faster when the drug loading is higher. In DuoCaplets the drug incorporated in the external layer is released first and there is a lag time until the release of the drug contained in the core starts depending on the characteristics of the external layer. The drug dissolution is driven by erosion-mediated process. Manufacture of different structured-shaped objects by 3D printing does modulate drug dissolution profiles of combinations of drugs and can be the future technology in the rational design of innovative dosage forms for personalised dose, with new specific pharmacokinetics characteristic or targeted to different sites of the gut.

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